REMARKS

Claims 1-3, 6-12, and 24-30 are all the claims pending in the application; each of the claims has been rejected.

Claims 6 and 10 have been amended to more clearly recite the invention of the present application, in view of the Examiner's rejection of the claims as being indefinite and non-enabled.

No new matter has been added. Entry of the amendment is earnestly solicited.

I. Formal Matters

A. Applicants note that an Information Disclosure Statement and Form PTO 1449 were submitted with this application on July 5, 2000. As Applicants have not yet received an initialed and signed copy of the Form PTO 1449, they now respectfully request return of an appropriately acknowledged copy of the form.

B. Applicants further note that the Examiner has not yet acknowledged perfection of Applicants' claim to priority. Therefore, Applicants now respectfully request that the Examiner acknowledge receipt of all of the priority documents, and perfection of Applicants' claim to priority.

II. Rejection of claims under 35 U.S.C. §112, second paragraph

At page 2 of the Office Action, claims 1-3, 6-12 and 24-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

A. The Examiner states that the use of the term "capable of" in each of the claims is indefinite because it is unclear how the biotinylated binding component is modified to be capable of binding the compound.

In response, Applicants have amended claim 6 (the only claim in which this term appears) to delete the term "capable of " from the claims.

In view of this amendment, Applicants assert that the rejection of the claims as being indefinite has been fully addressed and respectfully request reconsideration and withdrawal of this rejection.

B. The Examiner also states that the use of the term "crosslinked avidin" renders claims 1, 2, 6-12 and 24-30 unclear because this term can be interpreted in many ways such as many avidins crosslinked together since biotin binds to the avidin without the aid of a crosslinker, or that the avidin is bound to a linker which links the avidin and biotin together.

In response, Applicants assert that there is a clear discussion of the meaning of the term "crosslinked avidin" in the specification at page 7, lines 3-23. Therein, it is explained that because the four subunits of avidin may become disassociated at high temperatures, the avidin molecules may be crosslinked to prevent disassociation from occurring. It is further explained that one or more avidin proteins may be crosslinked together. In particular, Applicants point to lines 9-11 where it is stated that the cross-linked avidin is a protein in which "there exist crosslinkages at least between subunits, i.e., intramolecular crosslinkages."

Thus, Applicants assert that the term "crosslinked avidin" would have been clear to the skilled artisan reading the claims and specification.

In view of these comments, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Rejection of claims under 35 U.S.C. §112, first paragraph

At page 3 of the Office Action, claims 10 and 25 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that while the specification is enabling for an enzyme-biotin acceptor fused protein, it does not reasonably enable a biotinylated fused-protein of an enzyme and a biotin acceptor.

The Examiner goes on to state that the specification describes at page 3 that when a gene containing a luciferase gene and a biotin acceptor gene ligated thereto is expressed in a host cell, a luciferase-biotin acceptor fused protein is synthesized in a host cell. The specification does not teach that the biotinylated enzyme is a biotinylated fused protein of an enzyme and a biotin acceptor for biotin acceptor has many different meanings such as an avidin which can bind to biotin.

In response, Applicants note that claim 10 has been amended to more clearly state that the biotin acceptor recited therein is the portion of the fused protein that is biotinylated.

In view of the amendment to the claim, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. Rejection of claims under 35 U.S.C. §103

A. At page 4 of the Office Action, claims 1-3, 6, 7-9, 12, 24 and 27-30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Haughland et al. (U.S. Patent No. 5,443,986) in view of Giese (U.S. Patent No. 4,478,914).

The Examiner states that Haughland et al. teaches a biotin-avidin-biotin complex such as that recited in the pending claims, but does not disclose the use of crosslinked avidin.

The Examiner goes on to cite a new publication, Giese, that purportedly teaches the use of crosslinked avidin. The Examiner then states that it would have been obvious to one of ordinary skill in the art to use the crosslinked avidin of Giese in the method of Haughland et al. because the crosslinked avidin is more stable and has a higher biotin affinity than non-crosslinked avidin. The Examiner concludes by saying that the increased stability of the complexes would have a number of advantages such as longer shelf life, reducing shipping and storage problems and lower cost.

Finally, as to claim 8, the Examiner states that because Giese teaches that the second material is a biotin or biotin derivatives, Fc fragments, and combinations thereof, it would have been obvious to one of ordinary skill in the art to combine biotin and Fc fragments to detect antigen since antibody fragments such as Fc fragments efficiently bind to the antigen more specifically with high affinity.

In response, Applicants agree with the Examiner's position that Haughland et al. does not teach the use of crosslinked avidin. However, in contrast to the Examiner's position, Applicants assert that Giese does not cure the defect of Haughland et al.

The Giese reference discloses "cross-linked avidin" as a typical example of avidin derivatives at column 2, lines 9-11. However, there is no further discussion of crosslinked avidin or its properties. Indeed, there is no support for the Examiner's position that crosslinked avidin is more stable and leads to a higher-affinity binding substance. The only disclosure of such preferred properties of crosslinked avidin is in Applicants' specification. Thus, the Examiner is using improper hindsight to provide the motivation for using the crosslinked avidin of Giese in the biotin-avidin-biotin complexes of Haughland et al.

Thus, there is no teaching or motivation in either of the two references cited by the Examiner to combine the crosslinked avidin of Giese with the biotin-avidin-biotin complex of Haughland et al. There is no disclosure of improved properties of crosslinked avidin in Giese, therefore one of ordinary skill in the art would not have been motivated to replace the avidin used in Haughland et al. with that of Giese.

Accordingly, Applicants assert that the biotin-avidin-biotin complex, as recited in the rejected claims, is unobvious over Haughland et al. in view of Giese, and Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At page 5 of the Office Action, claims 10, 11, 25 and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Haughland et al. and Giese, further in view of Tatsumi (U.S. Patent No. 5,843,746).

The Examiner references his comments above on Haughland et al. and Giese, and states that these references fail to teach a biotin-introduced fused-protein of an enzyme such as a biotin-introduced luciferase.

With respect to Tatsumi, the Examiner states that the reference teaches a fusion protein (biotinylated firefly luciferase) which can be applied to a variety of bioluminescent analysis methods. Such a complex may be bound through the biotin moiety to avidin or streptavidin to form a luciferase complex.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the fused protein of Tatsumi in the combined method of Haughland et al. and Giese for detecting activity of luciferase since Haughland et al. teaches an enzyme immunoassay method

of using binding agent-biotin-avidin-biotin-enzyme and the luciferase enzyme of Tatsumi can be biotinylated.

The Examiner further contends that the biotinylated firefly luciferase of Tatsumi is more active and sensitive when compared to conventional chemically modified biotinylated firefly luciferase that is not in the form of a fusion protein. While the Examiner does not state that this fact as a motivation to combine, this appears to be his position.

In response, Applicants refer to their comments regarding the deficiencies in the disclosures of Haughland et al. and Giese, set forth above. As described therein, the biotin-avidin-biotin complex as presently claimed would not have been obvious to one of ordinary skill in the art over Haughland et al., in view of Giese.

Moreover, the Tatsumi reference does not disclose or suggest the biotin-avidin-biotin complex as set forth in the claims of the present invention. Specifically, Tatsumi does not teach the advantages of using cross-linked avidin.

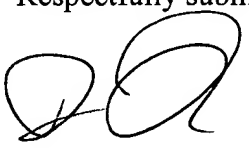
Applicants therefore assert that the invention recited in the rejected claims would not have been obvious over Haughland et al. and Giese, further in view of Tatsumi, and respectfully request reconsideration and withdrawal of this rejection.

V. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

6. (Twice amended) A method for analyzing a compound to be analyzed, said method comprising the steps of:

(1) providing a sample suspected of containing said compound to be analyzed;

(2) bringing into contact sequentially and in any order said sample, a biotinylated binding component that ~~capable of~~ specifically binds ~~binding~~ said compound, a crosslinked avidin, and a biotinylated labeling substance, to form a complex of said compound to be analyzed, said biotinylated binding component, said crosslinked avidin, and said biotinylated labeling substance; and

(3) analyzing a signal derived from said labeling substance in said complex.

10. (Twice amended) The analyzing method according to claim 9, wherein said biotinylated enzyme is a ~~biotinylated~~ fused ~~-~~protein of an enzyme and a biotinylated biotin acceptor.